

### REMARKS

Claims 25-27, 73-80, 83-88, and 94-130 are pending and subject to examination. Cancel claims 28, 82 and 90-93 without prejudice or disclaimer. The Examiner has withdrawn claim 89. Claims 26, 27, 29, 73-80, 84-88 are currently amended. Claims 94-130 are new. The newly added claims are claims that depend from claims already under examination and, accordingly, read on the elected invention.

Support for new claims can be found, e.g., as follows. Support for claims 94-104 can be found, e.g., at page 14, lines 2-3. Support for claims 105-109 can be found, e.g., in the original claims. Support for claims 110 and 111 can be found, e.g., at page 6, line 21. Support for claims 112 and 113 can be found, e.g., at page 13, lines 10-14. Support for claims 114-116 can be found, e.g., at page 27, lines 11-21. Support for claims 117-126 can be found, e.g., at page 49, lines 15-24.

Support for the remaining new claims can be found in the original claims and the specification. New claim 127 replaces, in part, and clarifies cancelled claim 28. Support for new claims 127-130 can be found, e.g., at page 41, line 13.

### Indefiniteness Rejections

The Examiner has rejected claims 26-29, 76, and 82 under 35 U.S.C. § 112, second paragraph for indefiniteness. The Applicants respond to the Examiner's paragraphs A, B, and C as follows:

A. The Applicants have amended claims that depend from claim 25 according to the suggestion of the Examiner.

B. The Applicants have cancelled claim 82 without prejudice or disclaimer.

C. Referring to claim 76, the Examiner asserted that:

It is unclear if the "portion" refers to any antibody portion or portions containing the antigen-binding domain of the antibody. Further, it is not clear what portion derived from a human antibody and what portion derived from non-human antibody.

One of ordinary skill in the art, on reading the specification, will realize that the term "portion" refers to a region that includes a functional unit of an antibody, for example, a framework region, a complementarity determining region (CDR), or a constant domain. This understanding is also supported by the specification at page 26, lines 3-18:

Additionally, recombinant anti-integrin antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, can also be used in the methods of the present invention. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in . . . Winter U.S. Pat. No. 5,225,539. . . .

Furthermore, these examples of "portions" are described in the references cited on page 26, lines 7-19 and incorporated by reference on page 55, lines 26-30. One such reference, U.S. 5,225,539, describes antibodies wherein the portions are constant domains (e.g., column 3, line 13), framework regions (e.g., column 4, line 19), CDRs (e.g., column 3, line 33), and those parts of a CDR crucial for antigen binding (e.g., column 3, line 34). Accordingly, the Applicants respectfully submit that indefiniteness rejection of claim 76 should be withdrawn.

#### Rejections for Lack of Written Description

The Examiner has rejected claims 25-30, 73-80 and 82-88 as new matter under 35 U.S.C. § 112, first paragraph:

The phrase "relative to a modified integrin I-domain in the closed conformation" claimed in claim 25, line 3, the phrase "relative to an integrin I-domain in the closed conformation" claimed in claim 30, line 3, the phrase "relative to an LFA-1 domain in the closed conformation" claimed in claim 75, lines 3-4, the phrase "but not to an integrin I-domain in the closed conformation" claimed in claim 83, line 2, the phrase "but not to a modified integrin I-domain that is locked in the closed conformation by the substitutions 289C/K294C" claimed in claim 84, lines 2-3, and the phrase "but not to a modified integrin I-domain in the closed conformation" claimed in claim 85,

lines 2-3, represent a departure from the specification and the claims as originally filed.

\* \* \* However, the specification does not provide a clear support for such limitations. The instant claims now recite limitations, which were not clearly disclosed in the specification and recited in the claims as originally filed.

The portion of the rejection regarding the phrase “relative to a modified integrin I-domain in the closed conformation” has been mooted by amending the claims 25 and 30. The Applicants do not concede that this phrase lacks written description. However, to expedite prosecution, the Applicants have amended claims 25 and 30 to moot the rejection, while reserving all rights to traverse the rejection and prosecute claims with the same or similar language in other applications or papers.

The written description rejection of claim 83 and claims dependent therefrom is respectfully traverse. Written description for an antibody that binds to “an integrin I-domain in the open conformation but not to an integrin I-domain in the closed conformation” can be found, e.g., at page 13, lines 24-27:

It is desirable that antibodies bind only to the active integrin conformation, e.g., the “open” conformation, because binding to the inactive conformation can lead to side reactions; . . . (emphasis added)

The above-quoted passage refers to antibodies that “bind only” to the active conformation in view of undesirable “binding to the inactive conformation.” The term “only,” particularly where juxtaposed with undesired binding to the inactive conformation, captures the meaning of “not” binding to the inactive conformation. MPEP 2163.02 states that “[t]he subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement).” At least this passage clearly describes antibodies that bind to an integrin I-domain in the open conformation “but not” to an integrin I-domain in the closed conformation.

Rejections for Alleged Lack of Enablement

The Examiner has also rejected claims 25-30, 73-80, and 82-88 under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Applicants respectfully traverse the rejection.

As the Applicants understand it, this rejection is premised on the Examiner's view that the claims were intended to cover the monoclonal antibodies listed in Table 2 on page 64 and Table 3 on page 69 of the specification. For example, the Examiner stated:

The specification on page 67, last paragraph discloses that the monoclonal antibodies BL5, F8.8, CBRLFA-I/9, May.03, TS1/22 and TS2/6 strongly inhibited binding of both wild type and mutant K287C/K294C, and the levels of inhibition to wild type LFA-I and the mutant were similar. Further the specification discloses that monoclonal antibodies TS I/11 and TS I/1 2 inhibited >90% binding of transfectants that express wild type LFAI, these antibodies showed reduced inhibition on binding of mutant K287C/D294C (40-60%). Furthermore, Monoclonal antibodies TS2/14, 25-3-I and CBRLFA-I/I show >90%inhibition on binding of wild type but had no to little inhibition on mutant K287C/K294C binding to ICAM-1. Finally, Table 3 in the specification at page 69, provides no single example of an antibody that binds the open conformation but not the closed conformation of the LFA-1. In the contrary Table 3, provides antibody that binds either to both closed and opened conformation or to the closed conformation but not to the opened conformation. The claimed products do not have the biological properties representative of what is being claimed, and applicant has not enabled any of these types of antibodies because it has not been shown that these antibodies are capable of functioning as that which is being claimed. [emphasis added]

The Examiner is correct to point out that none of the monoclonal antibodies listed in Tables 2 and 3 are within the scope of the claims. These antibodies were used to confirm the structural integrity of modified integrins, not as examples of antibodies with one or more claimed properties. Thus, at page 62, lines 23-26, the Applicants explained:

To test whether introducing the cysteines affected the overall conformation of the I-domain, a panel of monoclonal antibodies to different regions in the I-domain were tested for their reactivity with the I-domain mutants.

The Applicants also clarified, at page 63, lines 8-10, that these antibodies bind to the K287C/K294C (which mimics the open conformation) and L289C/K294C (which mimics the closed conformation) "equally well":

All of the antibodies, except for CBRLFA-1/1, bound to the mutants K287C/K294C and L289C/K294C and wild-type LFA-1 equally well (Table 2), indicating that the cysteine substitutions did not disrupt the I-domain structure.<sup>1</sup> [emphasis added]

Thus, Applicants have declared in the specification that these antibodies are not antibodies that “specifically bind[s] to a integrin I-domain in the open conformation” nor are they antibodies that bind “an integrin I-domain in the open conformation but not to an integrin I-domain in the closed conformation.” Thus, the disclosed monoclonal antibodies referred to by the Examiner are not examples of the claimed antibodies.

However, the lack of a described working example of an antibody is far from dispositive. See, e.g., MPEP 2164.02 (“The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation.”).

Since the level of skill the art of antibody production was high at the time of filing, one skilled in the art would have been able to produce the claimed antibodies, for example, using a modified integrin I-domain as an antigen for immunization or as as a target for screening a display library, or otherwise in any known method. Accord In re Wands, 858 F.2d 731, 740 (Fed Cir. 1988) (holding that claims to monoclonal antibodies were enabled in view of hybridoma technology as of a 1980 filing date); Hybritech Incorporated v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed Cir. 1987) (holding that sandwich immunoassay claims were enabled for antibody technology in view of Milstein’s hybridoma method and a 1983 filing date).

Further, the Applicants submit herewith a Declaration under 37 C.F.R. 1.132 by Dr. Edward Cohen, an employee of the licensee of the application. The Declaration describes an antibody, IgG#57, that “specifically binds to a modified integrin I-domain in the open conformation,” and that binds “an integrin I-domain in the open conformation but not to an integrin I-domain in the closed conformation.” Figure 1 (Exhibit B) shows that IgG#57 specifically binds to LFA-1 in which the I-domain is modified by K287C/K294C (an open conformation) when evaluated using surface plasmon resonance. IgG#57 does not interact with

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<sup>1</sup> The one exception, CBRLFA-1/1 had reduced binding to “the high affinity open mutant K287C/K294C” relative to wildtype and is also discussed *infra* p. 17.

an I-domain modified by L289C/K294C (a closed conformation) under similar conditions. Since the antibody was also made by a method described in the application, the IgG#57 antibody is evidence that one skilled in the art can prepare the claimed antibodies using a modified integrin I-domain.

Applicants respectfully submit that the rejections for lack of enablement should be withdrawn.

Rejection of Claims 25-27, 29-30, 73-80 and 82 under § 103

The Examiner has maintained the rejection of claims 25-27, 29-30, 73-80 and 82 in view of Huang and Lu. The rejection is respectfully traversed. The Examiner argues that the antibodies in Lu have the properties required by the afore-mentioned claims, namely that they specifically bind to an integrin I-domain in the open conformation. The claims require that the antibodies bind specifically to the open conformation, but the antibodies of Lu lack such specificity for the open conformation. The specification discusses the antibodies disclosed by Lu and notes that they differ in affinity for open and closed I domains by only a few percentage points. As explained below, the specification explicitly defines this level of differential binding as equivalent, and thus necessarily as a degree of specificity below that required by the claims. Thus, the antibodies disclosed in Lu cannot make obvious the claimed antibodies and antibody fragments.

The Applicants argued in the Response dated August 6, 2003 that, for Lu's antibodies, "binding to the open or closed conformational mutants is almost equivalent . . . or differs by only a few percentage points." The Examiner responded, at page 7 of the most recent action:

Applicant argues that the cell-to-cell differences for binding to the closed conformation and the cell-cell differences for binding to the open conformation are of similar magnitude as the differences between binding the open and closed conformation for the same cells-type. However, the comparison is still relative between open (modified) and closed (modified and unmodified).

Indeed, claims 25 and 30 require more than a marginal difference that is within the degree of experimental error. The Examiner appears to agree with this, at page 5:

Lu et al compare the binding of modified integrin I-domain in the open conformation (K287C/K294C) relative to the modified integrin I-domain in the closed conformation (L289C/K294C) as well as (see table I in particular) the wild type. The binding to the open and closed conformation mutants is almost equivalent among the antibodies or differs by only a few percentage points. [emphasis added]

Since the observed binding to open and closed conformation is “almost equivalent” for the antibodies described in Lu, it follows that these antibodies do not specifically bind to a integrin I-domain in the open conformation. Claims 25 and 30 require a degree of specificity that is more pronounced than “almost equivalent.” Indeed, at page 63, lines 8-10 of the specification, the Applicants defined the differences observed in Table 2 of the specification as “equal” and therefore, not as “specifically” binding:

All of the antibodies, except for CBRLFA-1/1, bound to the mutants K287C/K294C and L289C/K294C and wild-type LFA-1 equally well (Table 2), indicating that the cysteine substitutions did not disrupt the I-domain structure. Binding of monoclonal antibody CBRLFA-1/1 to the high-affinity open mutant K287C/K294C was reduced to 40-50% of wild-type, however, this antibody reacted with mutant L289C/K294C and the single cysteine substitution mutants K287C, L289C and K294C as well as wild-type.

Thus, as Applicants have used the terms, all the antibodies (except CBRLFA-1/1) in Table 2 bind “equally well” to mutants K287C/K294C and L289C/K294C. Since Table 2 of the specification largely provides the same information as Lu’s Table 2, this characterization of binding as “equally well” also applies to the data in Lu. As shown in columns 2 and 3 of the table below, the percentage differences in binding among these antibodies range, in absolute value, between 0-18%:

			K287/K294C		L289C/K294C	
ANTIBODY	%-293T	%K562T	293T	K562	293T	K562
BL5	7%	-6%	92	92	86	98
F8.8	12%	9%	94	102	84	94
TS2/6	8%	-7%	85	89	79	96
May.035	13%	-8%	93	93	82	101
TS1/11	0%	-9%	94	96	94	105
TS1/12	-13%	-18%	89	87	102	106

ANTIBODY			K287/K294C		L289C/K294C	
	%-293T	%K562T	293T	K562	293T	K562
TS1/22	5%	-15%	96	93	91	110
TS2/14	4%	-8%	86	95	83	103
25.3.1	2%	2%	93	88	91	86
<b>CBR LFA-1/1</b>	<b>-54%</b>	<b>-53%</b>	<b>44</b>	<b>56</b>	<b>96</b>	<b>118</b>
S6F1	-6%	13%	89	97	95	86
TS1/18	4%	-8%	100	97	96	106
YFC51	8%	-9%	103	101	95	111
CLBLFA-1/1	ND	-5%	ND	96	ND	101
May.017	ND	-2%	ND	109	ND	111
6.5e	ND	-13%	ND	84	ND	96
CBR LFA-1/7	3%	-2%	95	95	92	97
CBR LFA-1/2	ND	0%	ND	86	ND	86
YTA-1	ND	3%	ND	111	ND	108

Column 2 was calculated as (column#4/column#6 - 1).

Column 3 was calculated as (column#5/column#7 - 1).

Columns 4-7 were obtained from Lu et al.

Accordingly, a difference in the range of 0%-18% is, by definition, binding "equally well" to the open conformation and the closed conformation. Binding "equally well" to the open and closed conformations cannot amount to specifically binding to the open conformation. Therefore, the antibodies described in Lu (except CBRLFA-1/1) do not specifically bind to the open conformation as required by the claims.

The one exception, CBRLFA-1/1 is also illustrative. The Applicants noted at page 63, line 8, the CBRLFA-1/1 antibody does not bind "equally well," but appears to bind better to an I-domain in the closed conformation. Binding to the open conformation is reduced about 50% (see table above). Since the about 50% deviation by CBRLFA-1/1 is greater than 0%-18% range of values considered as binding "equally well," it follows that the Applicants excepted CBRLFA-1/1 from the category of antibodies that do not show specificity.

To summarize the results of Lu's Table 1 (also reproduced in the table above with percentage differences), all but one of the antibodies in Lu bind to an I-domain in the open conformation and to an I-domain in the closed conformation "equally well," and therefore do not specifically bind to the open conformation. The sole exception, CBRLFA-1/1 specifically binds



to the closed conformation. Since the antibodies in Lu do not specifically bind to an open conformation as required by claim 25 or claim 30, these antibodies cannot make obvious these claims or claims dependent therefrom. The Applicants respectfully request that the rejection be withdrawn.

#### Amendment of Claim 26

Claim 26 has been amended and is drawn to “an antibody or an antigen binding fragment thereof, which binds to an activation specific epitope on an integrin I-domain in the open conformation.” An activation specific epitope is necessarily absent from integrins that are in an inactive conformation. The known antibodies described in Table 2 of the specification bind with a substantial affinity to an integrin in an inactive conformation. See, e.g., columns 5 and 6 of Table 2 (also reproduced in the table above as columns 6 and 7), which document substantial binding to an LFA-1 protein locked in an inactive conformation by the L298C/K294C modification.

#### Conclusion

The Applicants respectfully submit that claims 25-27, 73-80, 83-88, and 94-130 are presently in condition for allowance, which action is respectfully requested. The Applicants do not concede any positions of the Examiner that are not expressly addressed above, nor do the Applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

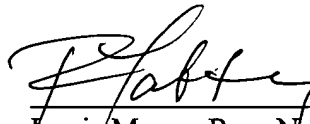
Applicant : Timothy A. Springer et al  
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Submitted concurrently herewith is a Petition for Three-Month Extension of Time.  
Please apply any other charges or credits to deposit account 06-1050, referencing attorney docket number 15775-029001.

Respectfully submitted,

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**PROFESSIONAL  
EXPERIENCE:**

DYAX, Cambridge, MA (1995-present)

**Senior Scientist / Investigator / Principal Scientist**

Co-inventor of a new method for capturing antibody diversity for construction of Fab phage display libraries. Constructed and directed others in the construction of a number of different peptide and small protein phage display libraries. Used and directed others in the use of phage display libraries for the selection and identification of a number of binding moieties to a variety of different target molecules (e.g., human serum albumin). Carried out small-scale production and purification of fusion proteins in *E. coli*.

CYTOMED, Cambridge, MA (1992-1994)

**Assistant Director, Molecular Biology**

Performed laboratory work on cloning and expression projects aimed at the development of therapeutics useful in the regulation of the complement system, T cell activation and other immune responses. Directed and advised others in cloning and expression research.

DIAGNOSTIC PRODUCTS CORPORATION Los Angeles, CA (1989-1992)

**Associate Director, Molecular Biology / Senior Research Scientist**

Performed laboratory work to develop a marker for human prostate cancer. Expressed portions of cDNAs encoding proteins from pathogenic organisms in bacterial systems for antigen production. Directed and advised others in cloning research.

INTEGRATED GENETICS, Framingham, MA (1983-1989)

**Staff Scientist**

Cloned cDNAs for expression of human therapeutic proteins in mammalian tissue culture cells (e.g., human protein S, a blood protein). Worked on expression cloning of a receptor molecule. Studied expression of human therapeutic proteins in yeasts.

FRED HUTCHINSON CANCER RESEARCH CENTER, Seattle, WA (1981-1983)

**Assistant Staff Scientist**

Studied transcription termination in the yeast *Saccharomyces*. Principal Investigator of NIH grant "Organization and evolution of *Drosophila* DNA".

PRINCETON UNIVERSITY, Princeton, NJ (1974-1981)

**Assistant Professor of Biology**

Principal Investigator of NIH grant "Organization and evolution of *Drosophila* DNA". Directed graduate and undergraduate students in research. Taught graduate level course in

Cell Biology. Taught undergraduate lecture course in Cell Biology and laboratory courses in Genetics and Developmental Biology as well as in Molecular and Cell Biology.

**EDUCATION:**

Post-Doctoral Fellow, Zoology Department, University of Washington (1972-1974)  
Research on eukaryotic chromosome structure performed in laboratory of Dr. Charles Laird

Ph.D., Biology Department, Yale University (1973)

Thesis topic: Biochemical characterization and cytological localization of repetitive DNAs in *Drosophila virilis* (Dr. Joseph Gall, thesis adviser)

M.Phil., Biology Department, Yale University (1970)

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**PUBLICATIONS:**

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- Wydro, R., Cohen, E., Dackowski, W., Stenflo, J., Lundwall, A. and Dahlback, B. Vector containing DNA encoding mature human protein S. United States Patent Number 5,258,288. Issued November 2, 1993.